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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/828,330	04/06/2001	Wayne P. Franco	388450.0002	5651

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EXAMINER
NICHOLS, CHRISTOPHER J

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 09/18/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/828,330	FRANCO, WAYNE P.	
	Examiner	Art Unit	
	Christopher Nichols, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 August 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16-53* is/are pending in the application.

4a) Of the above claim(s) *25-34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16-24 and 35-53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *16-53* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *06 June 2002* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 10 .
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other: .

DETAILED ACTION

Election/Restriction

1. Applicant's election of Group I (Claims 16-24 and 35-53), in part drawn to methods for treating coronary artery disease by administration of a growth factor in Paper No. 9 (8 July 2002) is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Claims 25-34 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Status of Application, Amendments, and/or Claims

2. The preliminary amendment of 8 August 2001 (Paper No. 6) has been entered in full. Claims 1-15 are canceled. Claims 25-34 are withdrawn from consideration, as discussed above. Claims 15-24 and 35-53 are under examination.

3. The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1647, Examiner Christopher Nichols.

Specification

4. The drawings contain handwritten figure numbers and the figures are unclear, as if they were distorted during facsimile transmission. Appropriate correction is required.

5. The Specification is objected to because of the following informalities: typo "Nos. **%,** 952, 008" (pp. 18 paragraph 00044). Appropriate correction is required.

6. The Specification is objected to because of the following pages are missing: pp. 40 (paragraphs 00099-000101), pp. 45 (paragraphs 000112-000114), pp. 50 (paragraphs 000125-000127), pp. 57 (paragraphs 000145-000147), and pp. 65 (paragraphs 000165-000168). The resulting gaps and sentence fragments must be corrected. However, the entry of new matter is not permitted. Support for all entry of new material to the specification must be supported as originally filed material (e.g. reference to specific pages of the priority document). Appropriate correction is required.

7. The Specification is objected to because of the following informalities: Colon missing from end of paragraph 000181 pp. 71 "...was calculated according to the formula" Appropriate correction is required.

8. The Specification is objected to because of the following informalities: Missing "%" from number on pp. 75 000191 "...LCX/LAD territory activity was 79 and 154% for..." and pp. 76 000191 "...LCX/LAD territory activity was 97 and 100% for..." Appropriate correction is required.

9. The Specification is objected to because of the following informalities: missing character " ...binding to –2 macroglobin..." (pp. 77 000195). Appropriate correction is required.

Claim Objections

10. Claims 17-24, 36-43, and 45-53 are objected to because of the following informalities: All dependent claims should only refer to a previous claim number. The addition of "(New)" is inappropriate and should be removed. Appropriate correction is required.

Sequence Rules

11. This application (09/828,330) does not comply with the sequence rules, 37 C.F.R. 1.825-1.825. There are disclosures of primer sequences on pp. 48 (paragraph 000119). Correction is required see "Notice to Comply" attached.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 16-24, 35-43, and 47 rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Claims 16-24, 35-43, and 47 are directed to methods of treatment of chronic or acute coronary artery disease wherein the amelioration of symptoms is achieved as the result of a clinically significant amount of angiogenesis wherein at least one administration of a growth factor is required to be by inhalation therapy. The specification teaches that angiogenesis a complex process that involves endothelial cell migration and proliferation, extracellular matrix

breakdown, smooth muscle cell proliferation and migration, formation and "sealing" of new vascular structures, and deposition of new matrix. While general guidance is provided regarding inhalation therapy of hormones, no working examples are provided re: inhalation therapy of growth factors. The art recognizes treatment of coronary artery disease by localized administration of angiogenic factors. The art teaches that growth factors including FGF-1 and VEGF affect a wide range of cell types (Slavin 1995; Jin et al. 2002). Collateral Therapeutics (WO 98/49300) teaches a method of using of acidic fibroblast growth factor (FGF-1) and/or basic fibroblast growth factor (FGF-2) to stimulate angiogenesis. In addition, Collateral Therapeutics (WO 98/49300) teaches the use of a pharmaceutical carrier for a composition contains one or both of FGF-1, FGF-2 and pharmaceutical compositions thereof. Collateral Therapeutics (WO 98/49300) teaches the use of said method when the patients suffering from ischemic condition. Collateral Therapeutics (WO 98/49300) teaches the use of vascular endothelial growth factors (VEGF), including pharmaceutical compositions thereof, as an angiogenesis agent for treatment of patients with ischemia. Collateral Therapeutics (WO 98/49300) teaches a method of administration of said growth factors via injection such as intramuscular, intravenous, intraperitoneal, subcutaneous, intrathecal or intracerebroventricular and conventional oral administration through such means as capsules, tablets, and liquid preparations as well as transmucosal means. Thus the claimed invention is directed to a systemic administration of growth factors for treatment of coronary artery disease, both chronic and acute, which is contrary to the teachings of the prior art. One skilled in this art would be expected to reasonably doubt that the claimed method would work due to the following obstacles: Expectation of angiogenesis along inhalation route (e.g. nasal cavity, throat, lungs); How do

growth factors get to heart in an effective amount?; Expectation of systemic angiogenesis? The specification does not provide guidance on how to overcome expected obstacles. Due to the large quantity of experimentation required to determine how to administer angiogenic growth factors by inhalation therapy to achieve angiogenesis effective to treat coronary artery disease, the specification's lack of guidance regarding how to overcome expected obstacles, the lack of working examples directed to such inhalation therapy, the contrary state of the art, the unpredictabili9ty of what is needed to overcome the obstacles, and the large breadth of the claims, undue experimentation would be required of the skilled artisan to practice the claimed methods.

13. Claims 44-46 and 48-53 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for administration of angiogenic growth factors and localized delivery, does not reasonably provide enablement for any growth factor and systemic delivery. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. A number of growth factors, including fibroblast growth factors (FGF) and vascular endothelial growth factors (VEGF) are integrally involved in the angiogenic response in ischemic conditions and in certain pathological states. The specification also teaches localized administration of angiogenic growth factors. The art recognizes treatment of coronary artery disease by localized administration of angiogenic factors. Whitehouse (USPN 6,440, 934) teaches a method of using rFGF-2 of SEQ ID NO: 2, or an angiogenically active fragment or mutant thereof, in a pharmaceutically acceptable carrier in a method for treating a human patient for coronary artery disease. Whitehouse teaches the use intravenous (IV), intracoronary (IC), and coronary catheter

delivery to stimulate angiogenesis. Whitehouse teaches this method for seen treating coronary artery disease and reducing post myocardial infarct injury in humans. Also, Whitehouse describes the use of FGF (fibroblast growth factors) in a mode of administration and dosages to human patients with coronary artery disease that provide the desired property of cardiac angiogenesis while minimizing adverse effects. The scope of patent protection sought by Applicant as defined by the claims fails to correlate reasonably with the scope of enabling disclosure provided by the specification and prior art for the following reasons.

14. Regarding use of all growth factors, the art recognizes that growth factors can have complementary and/or competitive physiological effects. Due to the large quantity of experimentation necessary to test all the applicable ratios growth factors, the lack of direction/guidance presented in the specification regarding evaluating growth factor effects on animal models, the absence of working examples directed to all growth factors, the complex nature of the invention, the unpredictability of the effects of growth factors on animals, including humans (Slavin 1995; Jin et al. 2002) and the breadth of the claims which fail to recite limitations for what effects any given growth factor would have on a patient, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

15. Claims 44-46, and 48-53 are rejected under 35 U.S.C. 102(a) as being anticipated by Merck & Co. Inc. (GB 2 332 373 A). Claims 44-46 and 48-53 are directed to methods of treatment of acute coronary artery disease wherein the steps comprise a) selecting a patient displaying symptoms of acute coronary disease, b) administering at least one dose of an effective amount of a first therapeutic growth factor protein formulation by a method of delivery that is the least invasive possible, consistent with the clinical condition of the patient, c) administering a second dose of an effective amount of a therapeutic growth factor protein formulation by a method of delivery that is the least invasive possible, consistent with the clinical condition of the patient. The second dose is optional. Merck & Co. Inc. (GB 2 332 373 A) describe use of their method comprising selecting a patient suffering from unstable angina, acute myocardial infarction, transient ischemic attacks and in a variety of other vasoocclsive disorders thus meeting the limitations of Claims 44, 48, and 50 (pp. 1 1-16). Merck & Co. Inc. (GB 2 332 373 A) also describe the administration of vascular endothelial growth factors such as VEGF-A (mature isoforms containing 206, 189, 165, 145, and 121 amino acid residues), the individual VEGF-A isoforms, VEGF homologues including VEGF-B, VEGF-C, VEGF-D, and placenta growth factor (PIGF), heterodimers composed of homologous VEGF subunits such as VEGF-A and either VEGF-B, VEGF-C, VEGF-D, or PIGF, and fibroblast growth factors such as acidic fibroblast growth factor (including stabilized mutated Ser 117 form of acid fibroblast growth factor) and basic fibroblast factor, either with or without an artificial N-terminal secretary polypeptides sequence, and combinations thereof, to use in stimulating angiogenesis in a patient having coronary or peripheral ischemic syndrome thus meeting the limitations of Claims 44-46,

49, and 51-53 (pp. 2-5; pp. 30 21-30). Merck & Co. Inc. (GB 2 332 373 A) describe the use any suitable means known to persons of ordinary skill in the art such as infusion or injection, e.g. intravenous, intraperitoneal, intramuscular, intraarterial, intralesional, continuous intravenous administration, or during surgery thus meeting the limitations of Claim 51 (pp. 3 14-25; pp. 27 3-15; pp. 31 10-21). It is noted that these methods of delivery have differing levels of invasiveness, with intravenous administration being less invasive than surgical. Merck & Co. Inc. (GB 2 332 373 A) describe the use of pharmaceutical compositions and dosing regimens that allow for multiple applications of angiogenesis stimulation factors such as FGF-1, FGF-2, VEGF, and combinations thereof, for treatment of patients thus meeting the limitations of Claims 44-46 and 48-53 (pp. 19-20; pp. 25 19-35; pp. 30 21-30).

Summary

16. Claims 16-24 and 35-53 are hereby rejected.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher Nichols, Ph.D. whose telephone number is 703-305-3955. The examiner can normally be reached on Monday through Friday, 8:30AM to 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz, Ph.D. can be reached on 703-308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications. The fax phone numbers for the customer service center is 703-872-9305.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Elizabeth C Kemmerer

CJN
September 12, 2002

Application No.: 09/828,330

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

- [X] 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to these regulations, published at 1114 OG 29, May 15, 1990 and at 55 FR 18230, May 1, 1990.
- [X] 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).
- [X] 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).
- [ ] 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."
- [ ] 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).
- [ ] 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).
- [X] 7. Other: The specification must make reference to the relevant sequence identifier (i.e., SEQ ID NO:) at each disclosure of a sequence embraced by the definitions set forth in 37 CFR 1.821-1.825.

Applicant Must Provide:

- [X] An initial or substitute computer readable form (CRF) copy of the "Sequence Listing". Alternatively, Applicant may request transfer of the CRF listing from the parent application if it is the same as that in the instant application. Please see attached Sample Request.
- [X] An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification. Applicant must provide this even if they choose to request transfer of the CRF.
- [X] A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216
For CRF Submission Help, call (703) 308-4212
For PatentIn software help, call (703) 308-6856

PLEASE RETURN A COPY OF THIS NOTICE WITH YOUR RESPONSE